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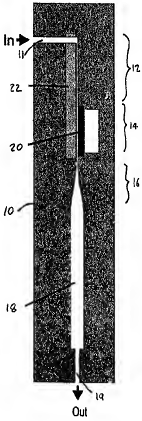
(54) Title: PARTICLE MANIPULATION

(57) Abstract

Fluid, in which particles are suspended, is passed along a duct (12, 14, 16, 18) having means (20, 22) for establishing an acoustic standing wave field so that the particles are displaced to form parallel bands. The duct includes an expansion in width (16) so that the spacing between the bands of particles is increased, so that these bands are easier to observe and/or to separate from the duct.



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Particle Manipulation

The present invention relates to an apparatus and method for performing the manipulation of particles suspended in a fluid, using an acoustic standing wave field.

When particles suspended in a fluid are subjected to an acoustic standing wave field, the particles displace to the location of the standing wave nodes. The effectiveness of this process varies with the relative densities and compressibilities of the particles and the suspending fluid.

A number of techniques have been proposed, using this phenomenon, to separate particles from a liquid or other fluid. Typically, the fluid is caused to flow through a duct in which an acoustic standing wave field is established, transverse to the length of the duct. The particles accordingly displace to form a series of parallel bands, and then a number of outlet passages are provided to lead the individual bands of particles away from the main flow duct. Because there are engineering difficulties involved in providing a parallel array of narrow outlet passages to collect the particle bands, the tendency is to operate at relatively low frequencies, so that the wavelength of the standing wave field is sufficiently large to provide an adequate spacing between the particle bands (half-wavelength spacing).

The primary acoustic radiation force on a single particle in an acoustic standing wave field is proportional to the operating frequency. Also the distance which a particle needs to move to reach a node decreases with increasing frequency (because the wavelength is smaller and hence the spacing between nodes is smaller). It is therefore easier to concentrate particles (including biological cells) at higher operating frequencies. Ultrasonic cavitation is also less likely to limit the applicable acoustic pressure at higher frequencies. However, the use of higher frequencies, and therefore smaller wavelengths, increases the engineering difficulties involved in providing outlet passages for the individual particle bands. In some cases, instead of separating particles from the suspending fluid, it may be

required to form the particles into their bands for the purpose of observation (e.g. for the purpose of an immuno-agglutination assay, as described in GB-2265004). For such cases, it will be appreciated that the particle bands are closer together at the higher frequencies, and therefore even more difficult to observe.

We have now devised an apparatus and method which overcome the difficulties noted above, and can be used whether the particles are to be separated from the suspending fluid or whether they are to be formed into their bands for observation purposes.

In accordance with the present invention, there is provided an apparatus for performing the manipulation of particles suspended in a fluid, the apparatus comprising a duct for the flow of a fluid in which particles are suspended, and means for establishing an acoustic standing wave field across the width of the duct, the duct being formed with an expansion in width downstream of the standing wave field.

In use of this apparatus, the particles in the fluid are displaced into a series of parallel bands by the acoustic standing wave field. The particles remain in these bands as the fluid flows downstream from the section in which the standing wave field is present. When the fluid reaches the expansion of the duct, the stream of fluid expands accordingly in width and in so doing the bands of particles are spread further apart, so increasing the spacing between adjacent bands.

In passing further along the duct, the particle bands retain their increased spacing. The bands can now either be observed, or they can be separated from the duct.

Preferably the duct includes an initial elongate section in which a laminar flow of the fluid is established, before the fluid enters the acoustic standing wave field.

The expansion of the duct is preferably formed by a section of the duct which progressively increases in width over the length of that section. Downstream of the expansion section, the duct preferably comprises an elongate section of uniform cross-section, in which the laminar flow of fluid is maintained.

It will be appreciated that by expanding the separation of the particle bands, these bands become substantially easier to observe and/or to separate from the fluid. Ultrasound of higher frequencies than hitherto can be used, preferably greater than 2MHz. Preferably means are provided downstream of the expansion section for observing the particle bands, or for separating them from the main duct.

The duct may be formed with at least one outlet passage which extends outwardly at an inclined angle, thus forming the expansion in width of the duct. The fluid adjacent the side of the duct from which the outlet passage diverges, and outwardly of the adjacent band of particles, now passes out of the duct along the outlet passage.

Preferably each outlet passage is provided with a valve. When the valve is closed, all of the fluid passes along the duct, without widthwise expansion and corresponding increased separation of the particle bands. As the valve is progressively opened, progressively more of the fluid is able to flow through the outlet passage, so effectively increasing the expansion of the fluid stream and passing an increasing portion of that stream out from the main flow duct. Alternatively or in addition, each outlet passage may be provided with a pump the flow rate of which is independently adjustable.

Also in accordance with the present invention, there is provided a method of performing the manipulation of particles suspended in a fluid, the method comprising causing the fluid to flow along a flow duct, establishing an acoustic standing wave field transversely of the duct, and providing a widthwise expansion of the stream of fluid downstream of the standing wave field.

Embodiments of the present invention will now be described by way of examples only and with reference to the accompanying drawings, in which:

FIGURE 1 is a diagrammatic longitudinal section through a first embodiment of apparatus in accordance with the invention;

FIGURE 2 is an enlarged diagrammatic view to show the manner in which the separation of the particle bands increases

over the expansion section of the apparatus of Figure 1; and

FIGURE 3 is a diagrammatic longitudinal section of a second embodiment of apparatus in accordance with the invention.

Referring to Figure 1, there is shown an apparatus which comprises a body 10 formed with a longitudinal duct or chamber, the chamber having four successive sections. Firstly, a straight duct of uniform cross-section forms a laminar flow stabilisation section 12 and the acoustic standing wave section 14. Next the duct expands in width, to form a stream expansion section 16. Then the chamber comprises a straight duct 18 of uniform cross-section, to form an observation section. An inlet passage 11 extends to the end of the first section 12 and an outlet passage 19 extends from the end of the observation section 18.

In the example shown, the duct forming the first two sections 12,14 has a rectangular cross-section of 1.1 x 10mm: the first section 12 has a length of 40mm and the second section has a length of 15mm. The third section 16 is also of rectangular cross-section, but expands from an initial size of 1.1 x 10mm to 8 x 10mm over a length of 30mm. The fourth section 18 of the chamber is of uniform rectangular cross-section, 8 x 10mm, and 65mm in length.

An acoustic standing wave field is established across the duct section 14 by a piezoelectric transducer 20 positioned on one side of the duct and a brass reflector 22 of 3mm thickness positioned on the opposite side of the duct. The transducer 20 comprises an air-backed transducer of 2.5cm diameter, type PZT 26 supplied by Ferroperm of Krisgard, Denmark, and having a fundamental resonant frequency near 3MHz. The back electrode of the transducer has been etched to an area of 1 x 1.5cm to restrict ultrasound generation to an area corresponding to the acoustic chamber.

In use, fluid with particles (which may be biological cells) in suspension is pumped through the chamber, preferably using a peristaltic pump. The first section 12 is sufficiently long to establish a stable laminar flow of the fluid. The acoustic standing wave field established in the second section of the chamber provides a number of nodal planes, spaced at

half-wavelength intervals across the width of the chamber between the transducer 20 and the reflector 22. Accordingly, the suspended particles displace transversely to these nodal planes, thus forming the particles into a series of parallel planar bands. As the fluid flows further along the chamber and out of the acoustic standing wave field, the particles remain in these bands: however, over the length of the expansion section 16 of the chamber, the bands B progressively separate, as shown in Figure 2. Then in flowing through the final chamber section 18, the bands B remain parallel to each other and at the expanded separation achieved in the expansion section 16 of the chamber.

It will be appreciated that because of the increased spacing between the adjacent bands B, these bands are very much easier to observe. Observation is achieved through a transparent side wall of the final section 18 of the chamber, i.e. in a direction perpendicular to the plane of the paper on which Figure 1 is drawn.

Alternatively or in addition, the principles of the invention may be employed for separating the particles from the fluid, for example in the manner shown in Figure 3. A duct 30 is shown in which firstly a laminar flow of the fluid has been established and then the acoustic standing wave field, through which the fluid flows, causes the suspended particles to displace transversely and so form a series of parallel bands B. The section of duct 30 which is shown in Figure 3 (and typically having a width W_1 of 1.6mm) is formed with a pair of outwardly-inclined outlet passages 32 (typically having a width W_2 of 3mm): these may be positioned at any desired longitudinal distance downstream from the acoustic standing wave field, because once formed into their bands B, the particles tend to remain in those bands for a considerable time. The outlet passages 32 form an expansion of the duct 30, causing the particle bands B to increase in separation: the fluid outside the outer bands of particles now passes out of the duct 30, through the outlet passages 32.

In the example shown in Figure 3, the duct 30 is formed with a second pair of outwardly-inclined outlet passages 34, at a position further downstream from the first pair of outlet

passages 32. This second pair of outlet passages 34 forms another expansion of the duct 30, causing the outer particle bands to pass out of the duct 30 through the passages 34. A third pair of outlet passages 36 are provided yet further downstream from the second pair 34, to form a third expansion of the duct 30 and causing the fluid either side of the remaining particle band to pass out of the duct 30. Figure 3 shows an arrangement in which three bands of particles are formed: however, it will be appreciated that in practice any number of bands may be formed (even just a single band), depending on the operating frequency and the width of the duct section across which the standing wave field is formed.

Each of the outlet passages 32,34,36 is preferably provided with a valve (indicated diagrammatically at V for one of the passages 36). For the passages 32, for example, when the corresponding valves are closed, no fluid can pass through those outlet passages, therefore the entire fluid flow continues along the duct 30 without the transverse expansion described above. By progressively opening the valves for the passages 32, a progressively higher proportion of the fluid is able to leave the duct 30. In this way, the valve on each outlet passage can be used to control the separation of fluid from the particles. Alternatively, each outlet passage may be provided with a pump of independently-variable flow rate, again so that the separation process can be controlled.

The fluid and particles which remain in the duct 30 may be subjected to a second stage of separation, to further enhance the particle content (or alternatively maximise the fluid separated from the particles).

Where desired, the duct 30 may include an expansion section between the section in which the standing wave field is established and the section (shown in Figure 3) which is provided with the outwardly-inclined outlet passages. This expansion section (corresponding to the expansion section 16 shown in Figure 1) provides some separation of the particle bands, enabling observation of these prior to entry into the section of the duct shown in Figure 3.

It will be appreciated that the invention may be used in a wide variety of applications, using a wide variety of

different particles or microparticles (including biological cells) in appropriate fluids.

Claims

1) An apparatus for performing the manipulation of particles suspended in a fluid, the apparatus comprising a duct (12,14,16,18) for the flow of a fluid in which particles are suspended, and means (20,22) for establishing an acoustic standing wave field across the width of the duct, the duct being formed with an expansion in width (16) downstream of the standing wave field.

2) An apparatus as claimed in claim 1, in which said duct includes an initial elongate section (12) in which a laminar flow of the fluid is established, before the fluid enters the acoustic standing wave field.

3) An apparatus as claimed in claim 1 or 2, in which said expansion of the duct is formed by a section (16) of the duct which progressively increases in width over the length of that section.

4) An apparatus as claimed in any preceding claim, in which the duct comprises an elongate section (18), downstream of said expansion, in which a laminar flow of said fluid is maintained.

5) An apparatus as claimed in claim 1 or 2, in which said duct is formed with at least one outlet passage (32) which extends outwardly at an inclined angle, thus forming said expansion in width of the duct.

6) An apparatus as claimed in claim 5, comprising a plurality of said outlet passages (32,34,36) spaced apart along said duct.

7) An apparatus as claimed in claim 5 or 6, in which the or each said outlet passage is provided with a valve (V)for controlling the flow of fluid through that passage.

8) An apparatus as claimed in any one of claims 5 to 7, in

which the or each said outlet passage is provided with a pump of adjustable flow rate.

9) An apparatus as claimed in any preceding claim, further comprising means downstream of said expansion for observing bands into which said particles are formed.

10) A method of performing the manipulation of particles suspended in a fluid, the method comprising causing the fluid to flow along a flow duct (12,14,16,18), establishing an acoustic standing wave field transversely of the duct, and providing a widthwise expansion of the stream of fluid downstream of the standing wave field.

11) A method as claimed in claim 10, comprising the step of establishing a laminar flow of the fluid before said fluid enters the acoustic standing wave field.

12) A method as claimed in claim 10 or 11, comprising the step of maintaining a laminar flow of said fluid along a section of said duct downstream of said widthwise expansion.

13) A method as claimed in any one of claims 10 to 12, further comprising the step of observing the fluid flow at a position downstream of said widthwise expansion.

14) A method as claimed in any one of claims 10 to 13, further comprising the step of separating fluid or particles from said duct at a position downstream of said widthwise expansion.

15) A method as claimed in any one of claims 10 to 14, in which said duct is formed with an outwardly-inclined outlet passage which provides said widthwise expansion, and further comprising the step of controlling a valve or a pump in said outlet passage to control said expansion of said fluid.

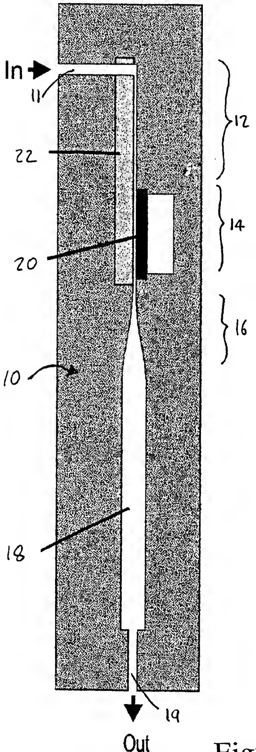

Figure 1

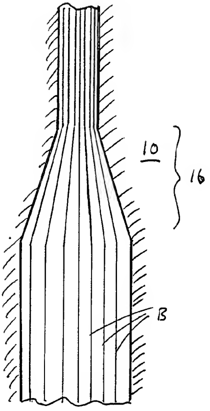

Figure 2

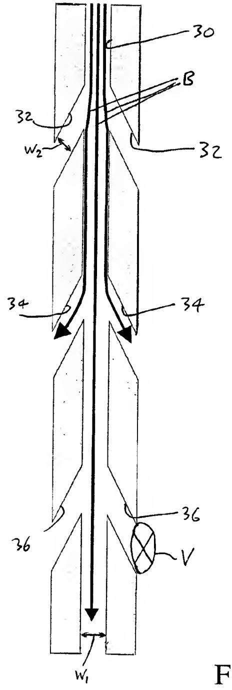

Figure 3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 98/01274

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 B01D43/00 B01D21/00 B01J19/10

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 B01D B01J C02F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	see the whole document	7,15
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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21 August 1998	01/09/1998

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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